

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Karin DRECHSEL et al :

Serial No.: 10/735,959 : Examiner: Mina Haghighatian  
Filed: December 15, 2003 : Group Art Unit: 1616  
For: INHALABLE FORMULATION OF A SOLUTION CONTAINING A TIOTROPIUM SALT

**REPLY BRIEF UNDER 37 C.F.R. §41.41**

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SIR:

This Reply Brief is submitted under 37 C.F.R. §41.41 in response to the Examiner's Answer, mailed September 16, 2010. Appellants maintain their reliance upon their Brief filed June 21, 2010. The following points are made for emphasis or clarification of points made in the Brief in light of the comments thereon in the Examiner's Answer and/or are made in response to new points of argument raised in the Examiner's Answer.

1. In the paragraph bridging pages 10-11 of the Examiner's Answer, it is alleged that the references teach using an acid to adjust pH, that it is obvious to adjust the pH to optimize stability and that appellants have not shown criticality of the claimed pH range. Appellants urge that the law does not support that one of ordinary skill in the art would consider conditions outside the scope of the general conditions taught by the reference for optimization. Freund '632 teaches that the pH of its compositions be within the range of 3.2 to 3.4. Given this specific requirement of Freund '632, one of ordinary skill in the art would not consider compositions with pH outside this range to optimize the compositions. Contrary to being considered optimizing, such would be expressly contrary to the reference teachings. The combined teachings of the references fail to establish a *prima facie* case of obviousness.

The primary reference Freund '632 specifically requires a pH range of 3.2 to 3.4 and the secondary reference only suggests a broader pH range for different compositions. Further, the allegation that appellants have not provided evidence of criticality or unexpected results for the claimed compositions is incorrect. Appellants provided data on the record showing the criticality of selection of a specific pH range for stability of the claimed tiotropium bromide compositions and further of the criticality of the combined features of the lower sodium edetate content and lower pH range recited in the claims and in providing an absence of spray anomalies (see Appellants' Brief, paragraph bridging pages 6-7 thru paragraph bridging pages 7-8 and the Evidence Appendix). The requirement of a higher pH range in Freund '632 is directly contrary to the advantages of the claimed pH range according to the invention. The preference to the higher pH and higher sodium edetate content in the references supports that the advantage of the claimed invention is unexpected.

2. At page 11, second full paragraph, of the Examiner's Answer it is argued that the minimum 3.2 pH value taught by Freund '632 is not distinct from the maximum 3.0 pH value of the claimed range absent evidence of unexpected results. Appellants respectfully disagree. The claimed pH range and the Freund '632 range clearly do not overlap and are distinct. The fact that Freund '632 requires such a specific narrow pH range of 3.2 to 3.4 strongly evidences that a pH of 3.0 is quite distinct. Additionally, as pointed out above, appellants have shown unexpected results for the select conditions of the claimed compositions.

3. At page 11, second full paragraph, the Examiner's Answer also relies on the In re Aller decision for the position that, when the reference discloses the general conditions, it is not inventive to discover optimum ranges within the general conditions by routine experimentation. The reliance on In re Aller is misplaced for two reasons. First, there is no overlap between the general conditions of pH disclosed by Freund '632 and in the instant claims. The broadest general pH condition disclosed by Freund '632 is a pH of from 3.2 – 3.4 which does not overlap the claimed range of 2.5 to 3.0. Thus, the facts are not analogous to In re Aller. To the contrary, the specific requirement of the 3.2 to 3.4 range in Freund '632 directs one of ordinary skill in the art away from claimed invention. Second, even if the facts were analogous, In re Aller does not preclude the ability of appellants to then establish patentability through a showing of unexpected results for a selection invention within the

generic teachings of the reference. As pointed out above, appellants have provided such a showing.

4. In the paragraph bridging pages 11-12 of the Examiner's Answer, it is alleged that the broader generic teaching of Freund '632 as to the amount of sodium edetate is sufficient to suggest compositions having the more selective amount of sodium edetate of the claimed invention. Appellants did not dispute that – contrary to the teachings regarding pH – the broadest teaching in Freund '632 regarding sodium edetate amount does overlap with the claimed range. Appellants' point in their Brief is that the preference in Freund '632 for the higher amount of sodium edetate – despite its broader generic teaching – shows that appellants' evidence showing an advantage for the smaller amount of sodium edetate was unexpected in view of the cited references. The preference to the higher amount in the references supports that the advantage of the claimed invention is unexpected.

5. At pages 12-14 of the Examiner's Answer arguments are made alleging that appellants' data showing unexpected advantages of the claimed invention is not convincing. Initially, appellants urge for the reasons previously stated that the references fail to establish a *prima facie* case of obviousness. Thus, the data are not necessary. The combined reference teachings fail to give one of ordinary skill in the art a reason to modify the specific 3.2 to 3.4 pH range requirement for the Freund '632 compositions. As for the Examiner's comments on the data itself, appellants have the following responses.

6. At page 12, first and second full paragraphs, of the Examiner's Answer, the Examiner points out, regarding Table 1, page 3, of Freund '632, that ipratropium bromide and tiotropium bromide are closely related compounds and that Freund '632 (and another patent) teach that compositions with higher EDTA (sodium edetate) levels have little or no spray anomalies. These points are in agreement with appellants' arguments. Appellants' point in the Brief was that, from the cited references, one of ordinary skill in the art would have expected that amounts of sodium edetate of 50 mg/100 ml or higher were desired to avoid spray anomalies. Thus, the showing by appellants (see the Table under the Sec. III. Results part of the Evidence Appendix to the Brief) that in the claimed compositions spray anomalies are reduced when a lower amount, i.e. 10 or 25 mg/100 ml, of sodium edetate is used was unexpected in view of the cited references.

7. In the paragraphs bridging pages 12-13 and pages 13-14, of the Examiner's Answer, it is argued that the data on spray anomalies is not consistent with any conclusion. Appellants respectfully disagree. The data establish that the compositions according to the claimed invention exhibited less spray anomalies when the sodium edetate content was below 50 mg/100 ml, i.e., at 10 or 25 mg/100 ml. As pointed out in point 5 above, this was unexpected in view of the prior art teachings. For a given pH, the spray anomalies are less when the sodium edetate is within the claimed range. This is unexpected (at any pH) from the prior art.

8. In addressing the spray anomaly data, the Examiner's Answer fails to comment on the other data provided by appellants. As pointed out in Appellants' Brief (page 6), appellant also provided evidence on the decomposition of tiotropium bromide at different pH values demonstrating that the selection of a specific pH range is critical for these tiotropium bromide compositions. See the first page of the Evidence Appendix. The data demonstrate that the stability of the tiotropium bromide compositions are strongly pH dependent in the pH range of 3.0 to 3.4 and that compositions at a pH of 3.0 – according to the claimed invention – are significantly more stable than compositions in the pH range of 3.2 to 3.4 – according to Freund '632. This fact is wholly unrecognized in the cited references. To the contrary, Freund '632 specifically requires the 3.2 to 3.4 pH range. The Examiner's Answer gives no reasoning why the decomposition data is not clear and convincing evidence of the unexpected properties and patentability of the claimed invention.

For the above reasons and the reasons set forth in Appellants' Brief, it is submitted that the decision of the Examiner finally rejecting claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95, on appeal, is in error and should be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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